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[REDACTED] EXAMINER

KAM, CHIH MIN

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1653

DATE MAILED: 09/16/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/750,022	ISAACS, INDU J.
Examiner	Art Unit	
Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 09 July 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-55 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 36,39 and 40 is/are allowed.

6) Claim(s) 1-35,37,38 and 41-55 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s). 13.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____

DETAILED ACTION

Status of the Claims

1. Claims 1-55 are pending.

Applicants' amendment filed July 9, 2003 (Paper No. 12) is acknowledged. Applicants' response has been fully considered. Claims 1, 14, 15 and 32 have been amended, and new claim 55 has been added. Therefore, claims 1-55 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 103

2. The previous rejection of claims 1-10, 22, and 49-54 under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* (WO 99/43361) in view of Makino *et al.* (U. S. Patent 4,985,244), is withdrawn in view of applicants' response at pages 3-5 in Paper No. 12.
3. The previous rejection of claims 11, 12 and 31 under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Makino *et al.* as applied to claims 1-10 above, further in view of Hora *et al.* (U. S. Patent 5,997,856), is withdrawn in view of applicants' response at page 5 in Paper No. 12.
4. The previous rejection of claims 13-15 and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Makino *et al.* as applied to claim 1 above, further in view of Drucker *et al.* (WO 97/39031), is withdrawn in view of applicants' response at page 6 in Paper No. 12.
5. The previous rejection of claims 16 and 21 under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Makino *et al.* as applied to claim 1 above, further in view of Thim

et al. (U.S. Patent 5,912,229), is withdrawn in view of applicants' response at page 6 in Paper No. 12.

6. The previous rejection of claims 43-46 under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Makino *et al.* as applied to claim 1 above, further in view of Drucker (U. S. Patent 5,952,301), is withdrawn in view of applicants' response at pages 6-7 in Paper No. 12.

Claim Objections

7. Claim 1 is objected to because the amended claim in the amendment filed July 9, 2003 (Paper No. 12) is not based on the previously amended claim 1 filed November 27, 2002 (Paper No. 8).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2-4, 17, 23-30, 34, 35, 37, 38, 41, 42, 44, 45 and 47-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 2-4, 34, 35, 37, 38, 44, 45, 50 and 51 are indefinite because of the use of the term "greater than about 6.0" or "greater than about 5.5". The term "greater than about 6.0" or "greater than about 5.5" renders the claim indefinite, it is unclear whether the pH of the formulation is greater than pH 6.0 (or 5.5), or less than pH 6.0 (5.5) as to "about". Claims 3, 4, 35, 38, 45 and 51 are included in this rejection for being dependent on rejected claims and not correcting the deficiency of the claims from which they depend.

10. Claims 23-25, for example, are indefinite because of the use of the term “less than about 5%”, “for up to at least 6 months” or “less than about 3 to about 4%”. The term “less than about 5%”, “for up to at least 6 months” or “less than about 3 to about 4%” renders the claim indefinite, it is unclear whether the water content in the lyophilized formulation is less than 5% as to “less than”, or greater than 5% as to “about”, whether the GLP-2 formulation is stable less than 6 months as to “up to” or greater than 6 months as to “about”, and the percentage of degradation of GLP-2 is in the range of 3 to 4% as to “about...to about”, or less than 3% as to “less than”. See also claims 26-30, 41, 42 and 47.

11. Claim 42 is indefinite because of the use of the term “no more than about 2%”. The term “no more than about 2%” renders the claim indefinite, it is unclear whether the water content is less than 2% as to “no more than” or greater than 2% as to “about”.

12. Claim 48 is indefinite because of the use of the term “up to about 24 hours”. The term “up to about 24 hours” renders the claim indefinite, it is unclear the GLP-2 formulation is stable less than 24 hours as to “up to”, or more than 24 hours as to “about”.

13. Claim 17 is indefinite because of the use of the term “one or more amino acid substitutions, additions, deletions or modifications” or “biological activity”. The term “one or more amino acid substitutions, additions, deletions or modifications” or “biological activity” renders the claim indefinite, it is unclear which amino acids are modified, and what amino acids are used for modifications, and what the biological activity is.

14. Claims 49-54 are indefinite because of the use of the term “a disorder, disease or condition” or “gastrointestinal disease”. The term “a disorder, disease or condition” or “gastrointestinal disease” renders the claim indefinite, it is unclear what disease is being treated.

Claims 50-54 are included in this rejection for being dependent on rejected claims and not correcting the deficiency of the claims from which they depend.

15. Claims 49-54 are indefinite because the claims lack essential steps in the method of treating a human or an animal having a disease using the GLP-2 formulation. The omitted step is the outcome for the treatment. Claims 50-54 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claims 1-10, 22, and 49-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* (WO 99/43361) in view of Yamazaki *et al.* (U. S. Patent 6,120,761, 102(e) date, December 16, 1998).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claims 1-4 and 10). The reference also indicates the concentration of the GLP-2 derivative is more than 0.5 mg and less than 100 mg/ml (page 4, lines 9-12; page 13, lines 16-19; claims 5-8), the formulation can be obtained in lyophilized form (page 13, line 10; claim 22), and the pharmaceutical composition can be

administered by injection or means of infusion pump to treat small bowel syndrome or intestinal inflammation (page 12, lines 13-16; page 13, 16-24, claims 49-54). However, Knudsen *et al.* do not disclose using histidine as a stabilizing agent. Yamazaki *et al.* disclose using 1-10 mg/ml of histidine (corresponding to 0.1-1%, w/v%) as a stabilizing agent in an erythropoietin solution preparation (column 1, lines 53-60; column 2, lines 47-58; column 3, lines 6-9; Fig. 3; Tables 4 and 5; claims 9 and 55). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare a pharmaceutical composition of GLP-2 as indicated by Knudsen *et al.* with the addition of histidine as a stabilizing agent as taught by Yamazaki *et al.* to treat a gastrointestinal disease because using histidine as a stabilizing agent is safe without the risk of viral contamination and is also economically advantageous than using the conventional stabilizer (column 4, lines 38-51). Thus, the combined references result in the claimed invention and was, as a whole, *prima facie* obvious at the time the claimed invention was made.

17. Claims 11, 12, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Yamazaki *et al.* as applied to claims 1-10 above, further in view of Hora *et al.* (U. S. Patent 5,997,856).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claims 1-4 and 10), the concentration of the GLP-2 derivative is more than 0.5 mg and less than 100 mg/ml (page 4, lines 9-12; page 13,

lines 16-19; claims 5-8), the formulation can be obtained in lyophilized form (page 13, line 10), and Yamazaki *et al.* disclose using 1-10 mg/ml of histidine (corresponding to 0.1-1%, w/v%) as a stabilizing agent in an erythropoietin solution preparation (column 1, lines 53-60; column 2, lines 47-58; column 3, lines 6-9; Fig. 3; Tables 4 and 5; claim 9). However, Knudsen *et al.* and Yamazaki *et al.* do not disclose the concentration of mannitol in the pharmaceutical composition. Hora *et al.* disclose 1-5% mannitol is used as a bulking agent in a protein preparation (column 25, lines 7-14). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art using the pharmaceutical formulation of GLP-2 analogs as indicated by Knudsen *et al.* and Yamazaki *et al.* with a known concentration of mannitol taught by Hora *et al.* (claims 11, 12, 31 and 33) to treat a gastrointestinal disease because the addition of a known concentration of mannitol can further improve the stability of the pharmaceutical composition. Thus, the combined references result in the claimed invention and was, as a whole, *prima facie* obvious at the time the claimed invention was made.

18. Claims 13-15, 17-20 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Yamazaki *et al.* and Hora *et al.* as applied to claim 1 above, further in view of Drucker *et al.* (WO 97/39031).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claim 1); Yamazaki *et al.* disclose using histidine as a stabilizing agent in a an erythropoietin solution preparation composition (column 1,

lines 53-60; column 2, lines 47-58; column 3, lines 6-9; Fig. 3; Tables 4 and 5) and Hora *et al.* disclose 1-5% mannitol is used as a bulking agent in a protein preparation (column 25, lines 7-14). However, Knudsen *et al.*, Yamazaki *et al.* and Hora *et al.* do not disclose the source and the sequences of GLP-2, the h[Gly2]GLP-2 analog, and DPP-IV-resistant GLP-2 analogs. Drucker *et al.* disclose the sequence of human GLP-2, h[Gly2]GLP-2 analog, and DPP-IV-resistant GLP-2 analogs, where the Ala at position 2 has been modified (page 7, lines 8-20; page 9, lines 11-22, Table 1). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art using the GLP-2 analogs taught by Drucker *et al.* to prepare the pharmaceutical composition as indicated by Knudsen *et al.*, Yamazaki *et al.* and Hora *et al.* (claims 13-15, 17-20 and 32) to treat a gastrointestinal disease because the use of DPP-IV resistant GLP-2 analogs in the pharmaceutical composition would result in a more stable pharmaceutical composition in vivo, where the GLP-2 analogs are degraded more slowly in vivo condition. Thus, the combined references result in the claimed invention and was, as a whole, *prima facie* obvious at the time the claimed invention was made.

19. Claims 16 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Yamazaki *et al.* as applied to claim 1 above, further in view of Thim *et al.* (U.S. Patent 5,912,229).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claim 1), and Yamazaki *et al.* disclose

using histidine as a stabilizing agent in a an erythropoietin solution preparation composition (column 1, lines 53-60; column 2, lines 47-58; column 3, lines 6-9; Fig. 3; Tables 4 and 5). However, Knudsen *et al.* and Yamazaki *et al.* do not disclose the use of GLP-2 receptor to identify peptides that bind GLP-2 receptor or as GLP-2 receptor antagonist. Thim *et al.* disclose a GLP-2 receptor is identified and cloned, and a cell line stably expressing the receptor is used in a screening assay to identify the antagonist of GLP-2 receptor (column 10, lines 43-59). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art using the GLP-2 analogs taught by Thim *et al.* to prepare the pharmaceutical composition as indicated by Knudsen *et al.* and Yamazaki *et al.* (claims 16 and 21) to treat a GLP-2 receptor-associated disease because the GLP-2 receptor antagonist can be used to treat GLP-2 receptor-associated diseases. Thus, the combined references result in the claimed invention and was, as a whole, *prima facie* obvious at the time the claimed invention was made.

20. Claims 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Yamazaki *et al.* as applied to claim 1 above, further in view of Drucker (U. S. Patent 5,952,301).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claim 1), and Yamazaki *et al.* disclose using histidine as a stabilizing agent in a an erythropoietin solution preparation composition (column 1, lines 53-60; column 2, lines 47-58; column 3, lines 6-9; Fig. 3; Tables 4 and 5).

However, Knudsen *et al.* and Yamazaki *et al.* do not disclose a kit comprising a lyophilized GLP-2 formulation. Drucker disclose a kit comprising GLP-2 or GLP-2 analogs (column 2, lines 56-61). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art using the pharmaceutical composition as indicated by Knudsen *et al.* and Yamazaki *et al.* to prepare a kit as taught by Drucker (claims 43-46) to treat a gastrointestinal disease because the kit containing the pharmaceutical composition can be used more conveniently in the treatment. Thus, the combined references result in the claimed invention and was, as a whole, *prima facie* obvious at the time the claimed invention was made.

Conclusion

21. Claims 1-35, 37, 38 and 41-55 are rejected. It appears that claims 36, 39 and 40 are free of prior art.

A telephone call was made to Attorney, Michele Simkin on September 15, 2003 regarding the allowable subject matter (see Interview Summary), however, applicants indicate they want to review the Office Action before making any decision.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8:00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. *cmk*
Patent Examiner

September 13, 2003

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